AstraZeneca

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5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket No. 99D-1454
Comments on draft Guidance for Industry

Please submit the attached comments from AstraZeneca LP to Docket No. 99D-1454 in response to the draft guidance entitled, "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing, and Controls Documentation" which was published in the *Federal Register* on June 2, 1999.

Please direct any questions to me at 61 0-695- 1263, or, in my absence, to Robert Monaghan, Regulatory Project Manager at 610-695-4227 or Diane Alleva, Ph. D., Director, Product Operations at 610-578-8845.

Sincerely yours,

Eric Couture

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Attachments

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COMMENTS ON DRAFT GUIDANCE FOR INDUSTRY,
"NASAL SPRAY AND INHALATION SOLUTION, SUSPENSION, AND SPRAY DRUG PRODUCTS"

General Comments

- Many parts of the guidance overlap with ICH requirements, e.g. Sections Cl, Active Ingredient, Section F, Introductory Paragraph, Section Fld, Impurities and Degradation Products, Section H, Drug Product Stability. It is strongly recommended that the document cross reference ICH guidelines rather than interpreting and adding to the requirements outlined by ICH. In many cases, more restrictive regulatory policies are outlined than those agreed upon by ICH. This is contrary to the spirit of and agreements reached in ICH.

- Since the guidance covers different related product types (i.e. nasal spray and inhalation solution, suspension, and spray drug products), there are a number of references where further clarity is required with regard to the application of certain principles or clauses to the different product types. For example, drug products in this guidance can be classified as unit dose or multi-dose. A significant portion of the document as written is more applicable to multi-dose products rather than unit dose. It is recommended that the Agency further clarify the requirements for unit dose versus multi-dose products.

- The document contains a great deal of "educational and background information" that seems unnecessary for guidance on Chemistry, Manufacturing and Controls Documentation. The document would be easier to use if it simply stated the additional CMC documentation that would be required for these dosage forms, above and beyond what is already required according to existing guidances. Since this guidance is relatively similar to the guidance issued for the MDIs and DPIs, it might help industry to have just one guidance that covers all products, highlighting the different requirements for each specific dosage form.

- Additionally, the document also includes many comments that are really cGMP concerns. It would be more helpful to focus on regulatory requirements specific for nasal and inhalation products.

- None of the sections involving leachables/extractables specify that this testing is needed only for components that have product contact.

- We recommend that LABELING CONSIDERATIONS be placed in a different guidance since labeling is not CMC documentation although it is submitted in the CMC section of an NDA.

- In general, this should be a document that covers the requirements for first approval of a product, and Post Approval changes should be covered in a "SUPAC-type" guidance or in a specific section for post-approval changes. It is confusing to include pre-approval requirements and post-approval requirements sometimes in the same section.

- For the container/closure system and for the sections on stability, it would be helpful if these could refer to the already existing guidances on these subjects. Having general guidance documents on a subject, such as stability, which covers all dosage forms would be beneficial and less confusing. Which guidance is the appropriate one to reference when the same information is covered in more than one guidance?

- In general, the level of control of excipients is not consistent with other products, and is stricter than those for parenteral products. We believe that excipients for these types of products should be treated in the same manner as for parenteral products.

Specific Comments

Line	Comment
8 - 9	Please clarify the application of recommendations in this guidance to products in the IND stage of development.
68 - 70	Sterilization of suspensions may not be technically feasible. Please suggest acceptable alternative approaches.
125 -132	This section recommends more detail than is necessary and is overly restrictive. The idea that each component should be identified by its established name, chemical name, structural formulas, and a description statement of its composition is not necessary. Most components commonly used in industry have a historical basis for their use.

136 - 147 This section on composition describes details that are typically part of the CMC section of the NDA. These details do not need to be reiterated here since they are not unique to nasal or inhalation drug products.

144 - 145 It may also be necessary to include excesses to cover deposition on the pump / plastics, etc. (in addition to the manufacturing losses specified).

159 - 207 The section seems very tutorial in nature, and more detailed than necessary for a guidance.

163 - 169 This paragraph describes information that would be gathered during preformulation so we suggest it not be included in the section on specifications. The next paragraph addresses drug substance parameters that should be included in its specification.

171 - 178 We recommend that the specification for drug substance should also contain acceptance criteria and tests for impurities / degradation products.

The requirements outlined here for API specifications are summarized in lines 171-173. The remainder of this section seems to contain unnecessary details.

180 - 183 We suggest that crystalline form (e.g., shape, surface texture) should be included in preformulation work but not be part of the active ingredient specification.

Please clarify how “surface texture” is defined in this context and how it would be measured / evaluated.

183 - 188 This section describes laser diffraction methodology for testing particle size distribution. The details of how to scientifically justify the use of this method are unnecessary for this guidance.

189 - 191 We suggest that amorphous form should be included in the pre-formulation work but not be part of the specification. We also suggest that amorphous content can be included as an in-process control but not form part of the overall specification.

196 - 198 We recommend that a reference be made to ICH guideline Q3 A (Impurities Testing Guideline: Impurities in New Drug Substances).

209 - 275 The logic of this section relating to excipients would be improved by placing the second to last paragraph (page 7, lines 258-267) as paragraph 1 and the last paragraph (page 8, lines 269-274) as paragraph 2. Lines 233-243 on page 7, are redundant and should be linked to the last paragraph of this section.

223 Batch analysis data should only be required for non-pharmacopoeia1 excipients. We suggest this requirement be deleted.

224 - 226 Submission of data supporting postapproval changes of excipient suppliers when the material meets specifications seems overly restrictive and contrary to traditional industry practice.

233 - 243 Reference to the USP or NF should be enough to describe compendia1 excipients. It is unclear whether these requirements apply to solution nasal sprays. If so, we believe that requirements beyond reference to compendia are too restrictive and should be deleted.

245 – 256 This paragraph is mostly cGMP-based information. Since the CFR reference is already provided, it appears redundant.

This information would typically be covered by a sponsor's vendor assurance program. This information should not be included in the guideline; moreover, the vendors' test results should not be required for submission, but be available for inspection.

245 - 249 Confirmation is requested that verification of testing may be carried out by other means other than by repetition of the tests by the applicant. It is sometimes not practical or desirable to repeat testing in-house due to requirements for specialized equipment, or capability to handle highly toxic impurities. Normal means of assessment of capability should suffice. For example, regular audits of the supplier, review of results supplied and performance of material, testing of "spiked" samples, etc.

269 - 275 We agree that testing in addition to that in the pharmacopoeia may sometimes be required. However, pharmacopoeia1 materials can only be purchased to the pharmacopoeia1 grade. Pharmaceutical companies do not purchase materials in sufficient quantities to influence suppliers to change the quality of material.

For polymers, there will be inter-batch variation in molecular weight distribution. As part of formulation development, it is possible to test batches with different molecular weight distributions to demonstrate that this parameter does not affect drug product. However, suppliers will not tailor make batches to a tighter molecular weight distribution. Specification limits should be set based on development work and commercial availability.

284 - 285 This section requires that each excipient manufacturer should be identified by name and address. This information is not typically submitted, since the name and address of the supplier do not add any information about the quality of the excipients.

If compendia1 excipients are used, a change in supplier should be an annual reportable change.

292 – 294 In this paragraph, it is stated that inhalation solutions, suspensions and spray drug products should be manufactured as sterile products. Is this always necessary when these products may be used in a non-sterile device?

287 - 338 This entire section (Method(s) of Manufacture and Packaging) is adequately described by guidance for the CMC section of an NDA and to some extent by 21 CFR 314.50. Its appearance in this guidance is redundant.

295 – 302 This paragraph pertains to drug substance, therefore, it should be moved to the drug substance section of the guidance.

304 - 309 21 CFR 314.50 does not require submission of completed batch records for representative clinical batches, only biobatches and primary stability batches. What is the rationale for including completed batch records?

The option to include a completed batch record OR a detailed description of the manufacturing process should be provided. The submission of a detailed description may eliminate the need for constant updating of the filing as the result of only minor changes to the master batch production record.

315 - 319 We would suggest that differentiation is made in this paragraph between routine in-process testing and process validation.

Delivery performance may be tested at any time before the release of the batch; it does not need to be tested in process.

326 - 328 Testing for seal completeness and for seal strength may not be technically feasible. Suggestions are requested for how to test sealing properties. We believe that process validation and in-process controls ensure seal completeness.

333 – 337 The work on leachables should be demonstrated during formulation development only.

These two sentences are confusing -the first (333) states that absence of leachables must be shown and the second (335) states that leachables must be qualified. Are leachables from labels being treated differently from other leachables?

342 The section on “Specifications for the Drug Product” specifies that an analytical sampling plan be provided. This is a cGMP issue and we strongly recommend deleting this requirement.

351 Clarification is requested whether “clinical” indicates Phase III clinical studies. It is possible that not all test methods would be completely validated prior to Phase III.

360	Clarity testing should be conducted when applicable. Suspension products may not be able to "pass" a clarity test.
360 - 367 and 605 - 607	This section deals with color of a nasal spray product (and of inhalation solutions, suspensions, and sprays) and requires that a quantitative test, with acceptance criteria, be established for drug product with color associated with the formulation. We believe this is an inflexible approach. Product quality can be assured through alternative tests; e.g., control of impurities and degradation products in the drug product specification based on assessment of stability data.
374	The identification for active ingredient will confirm chirality. For the drug product, we believe that a test to confirm chirality should be included during development of the formulation.
379	This paragraph refers to assay of drug substance in the entire container. For a unit dose product, this clause should apply to delivered product rather than to entire container. The assay of delivered product is more scientifically correct as this is the dose that the patient will receive.
388	In accordance with ICH, only degradation products should be included in drug product specifications.
392 - 393	This sentence discusses specifying impurities "at levels of 0.1 percent or greater." This is not in agreement with ICH requirements which state reportable impurity levels are "greater than 0.1 percent." We strongly recommend that the Agency adopt ICH requirements. It is requested that a reference be made to ICH guideline Q 3 B (Impurities Testing Guideline: Impurities in New Medicinal Products).
397	This section needs to add a correlation of this preservative/stabilizing excipient assay to the performance of the product in PET testing.
404	Pump Delivery should be a component release test, not a finished product test. One should determine before product is manufactured that the pump is functioning properly.

406 - 413 Also, for pump delivery a dose weight should represent the number of sprays specified in the labeling.
A second tier test should be added.
Pumps less that 100 microliters / dose will generally not conform to the proposed limits. For these pumps, wider limits should be considered.

How much data on the pump performance is expected from the pump manufacturer?

In assessing pump-to-pump reproducibility for a unit dose product, "delivery from" rather than "metering ability of the pump" is more appropriate.

415 – 474 These two sections appear to be redundant testing. If it is important to understand SCU through Container Life, then only test as outlined in Section h.

1/ Correlation to proposed valve specification. Only an extra 5% is allowed above mean (+10%) or individual (+15%) for the product. The variation will include;
. Suspension concentration;
. Suspension concentration increase through can life;
. Actuator deposition;
. Analytical variation
2/ The limits for dose uniformity should be modified to 25/35.
3/ Mean dose should be removed or a second tier test added.

422 - 423 For systemic administration, the number of actuations constituting a dose should include both nostrils.

423 – 425 The requirement to ensure that in vitro dose collections are reproducible may be forcing the industry to develop robotic methods for testing of these products. Line 424 suggests that only automated procedures are acceptable; is this the true intent of the Agency?

417 - 418 and 435 - 447 In the case of a unit dose product, the limits applied to pump delivery (section f; lines 411 - 413) and spray content uniformity (section g; lines 435 - 447) should be the same. Furthermore, if the Agency amends drug assay (section c) to conform to delivered product, rather than entire container (see comment line 379), and spray content uniformity is applied, effectively pump delivery (section f) is no longer required.

423 - 425 This sentence describes actuation parameters required for reproducibility of "in-vitro dose collection." It is suggested that unit dose products do not need actuation parameters. Certain unit dose devices use a system based on a pressure point to "fire" the pump; in such circumstances, firing is based on inertia of the actuation finger and therefore more independent of specific actuation parameters.

435 – 447 The specifications presented within this section are not consistent with those outlined in USP. We recommend adopting USP specifications,

438 - 462 The fact that if the mean is outside $\pm 15\%$, this does not lead to 2^{nd} tier testing indicates a view that this is a uniformity requirement and not a requirement on mean. In our view, the requirements for uniformity and mean are being confused. This is particularly the case for the Spray Uniformity Through Container Life test, where the measured mean is based on only 2 doses for each point in the container life. We therefore suggest that a potential failure for the mean in the 1^{st} tier should be followed by 2^{nd} tier testing to verify or falsify that there is a problem with the mean.

478 - 502 Spray pattern is determined on incoming batches of components using methylene blue. It is then part of formulation development to demonstrate correlation between results using methylene blue and using product.

The significance of these in vitro tests for the evaluation of a drug product can be questioned. We believe that the extent of the proposed testing should be reduced, such as use only the most discriminating distance.

This section on spray pattern / plume geometry does not take into consideration that some unit dose devices, based on a pressure point system, give a more reproducible spray pattern than other systems. In this case, spray pattern can be controlled through testing of components rather than testing the finished product, provided than an acceptable level of variation has been established through testing of stability and clinical batches during development. Further, it seems that this is an unnecessary requirement for unit dose products.

We believe the reference to spray pattern determination specific for drug substance is overly restrictive and should be deleted. Where the drug substance is in the plume pattern is an irrelevant detail when uniformity of dose is assured by other tests.

The requirement for uniform density of the spray pattern can be

questioned. The physical principal behind the generation of the spray will generate spray patterns where the color intensity decreases from the center of the spot to the periphery.

Further, the guidance provides details about training of the analyst performing this test which is a cGMP concern. We recommend deleting this.

497 - 499 The specified range for the ratio of the longest to the shortest axis should be established based on distance(s). The proposed range (1.00-1.20) does not reflect the actual performance of the spray pumps in current products. A range of 1.0-1.8 is more realistic.

504 - 513 Our previous comments on spray pattern testing apply here for droplet size testing, for a unit dose system, based on pressure point actuation, where a more reproducible droplet size distribution is produced compared with other systems. In this case, droplet size can be controlled through testing of components rather than testing the finished product, provided than an acceptable level of variation has been established through testing of stability and clinical batches during development.

506 - 517 The significance of these in vitro tests for the evaluation of a drug product can be questioned. We believe that the extent of the proposed testing should be limited.

This section contains too many details that are unnecessary for a guidance document.

515 – 536 Section k addresses the particle size distribution of the product, therefore, section 1 (Microscopic evaluation) appears to be redundant testing.

Microscopy is a valuable tool during development, but it is not required for a release specification. Large particles, agglomerates and crystal growth of the drug will be shown in the particle size distribution. If this test is not deleted, suggestions are requested on appropriate procedures other than microscopy.

538 - 544 and 637 - 640 It is not necessary to include a foreign particulate section providing an acceptable in process assessment of foreign particulates is performed. Line 543-544 states that “levels of foreign particulates may increase with time, temperature, and stress”; this adds a new stability requirement and is restrictive.

546 - 557	We believe that this should only apply to multidose products with preservative. In the microbial limits section, it is stated that appropriate testing should show that the drug product does not support the growth of microorganisms. If microbiological quality is maintained throughout the expiration dating period, it is not necessary to demonstrate that a drug product does not support the growth of microorganisms.
580 – 591	Leachables should be determined during development, and once the levels are established, there is no need to continue to monitor this during stability. It should only be necessary to test for them on stability if a change is made to an elastomeric closure or plastic component, or to the coating of the container or the label.
593 – 596	This should be noted as a stability requirement.
598 – 601	This should be noted as a release requirement only.
593 - 596 and 642 - 644	Please clarify the pH statement in this section. "Apparent pH" applies to suspension products and "pH" applies for solution products.
598 - 601 and 646 - 648	Osmolality should not change for a drug product with a defined formulation. We recommend deleting this test.
615 – 617	The reference to nasal sprays should be the only information provided in this section. The remaining information is redundant.
678	A definition of the "mouthpiece" is required.
694 - 715	Please provide an explanation of why Plume geometry is more important for inhalation sprays. Plume geometry should be performed only as part of formulation development.
717 – 788	This section appears to be a tutorial on methods development. This does not seem appropriate for inclusion in this guidance.

746 All analytical equipment is qualified, but this information is not required in the application, so it is not clear why cascade impactor qualification should be treated differently. If this information is required in the application, confirmation is requested that a definition of the criteria is sufficient and data are not required.

761 The guidance seems to suggest that impactor mass balance should be judged by comparing the total dose found in the impactor to the label claim delivered dose and not the actual average delivered dose for the sample in question. If this is the case, then it is not a mass balance parameter in the true sense of the word. Further, it does not seem reasonable to expect that the dose recovered from the impactor (which may be a few actuations for a low potency drug) must also comply with the suggested specifications for content uniformity/average delivered dose.

We believe it more sensible to keep the mass balance criteria pure, i.e., to compare the dose recovered from the impactor to the average dose recovered from the dose collection apparatus and use the internationally harmonized +/- criteria of the pharmacopoieas.

811 - 812 Please explain if the intention of including this statement is to establish dose-counting mechanisms as an expected feature, specifically if a justification will be required if such a mechanism is not incorporated.

812 - 816 Do replaceable reservoirs have to be drug/strength specific?

For DPIs and pMDIs it appears that the requirement for the device to be specific for the intended formulation reservoir only is met by color coding. Is color coding sufficient for the formulations covered by this guideline? More clarification is requested on what kind of mechanism should be included.

796 - 816 This section clearly applies to multi-dose products. Please provide an exclusion for unit dose products.

827 - 839 While it is recognized that, in general, less data is needed for an ANDA, in this instance, there seems to be extreme differences between the requirements for leachables in an NDA and an ANDA. Please provide a rationale of why this is so.

830 At line 799, the container and closure system definition includes protective packaging. It is assumed that extractives/leachables testing is not required for secondary protective packaging.

831 - 832 The phrase "may obviate" should be more definitive, so that it is obvious that if the applicant provides the correlation, they will not be required to monitor leachables during routine stability testing.

850 We request that a definition of "source" (for each part of the container and closure system) be included.

854 Clarification is needed regarding how to interpret "schematic engineering drawings" and "dimensional measurements", i.e. the level of detail required.

855 We suggest that only the "critical" dimensions be included.

860 Extractable testing should be performed during development but not considered routine testing.

873 - 875 The tolerances required for dimensional measurements of critical components should be established during development. Very tight tolerances for dimension do not necessarily improve the performance of a component.

881 "Contact with patient" – does this mean patient hands or just mucosal membranes?

885 - 887 We recommend that only assembled components should be submitted (not disassembled components).

891 - 905 Control extraction studies should be necessary only for critical components in contact with the formulation or patient (nosepiece). Please add an explanation as to what level the qualitative extractable profile is expected to be determined.

This section on control extraction studies should be rewritten to reflect a difference in development studies (forced extraction) appropriate to determine a potential extraction process suitable for routine application and the routine test itself. Extracts from proposed extraction studies are only those which should be evaluated toxicologically (lines 904-905).

900 - 908 It should not be necessary to do extraction studies with high stress. solvents – only relevant solvents should be evaluated. It should not be necessary to identify all extractables.

904 - 922 A unit dose product contained with a unit dose vial, fitted with a rubber stopper, does not need to undergo toxicological qualification. The results of USP Biological Reactivity tests (USP <87> and <88>) are sufficient. Moreover, toxicological extraction studies should be part of the developmental pharmaceutics studies.

926 - 937 Please clarify that this section is not required for unit dose products.

929 This asks for "routine" testing of extractables. Once these are established, extractables should then be controlled at the component supplier, and new extractables testing should only be required if a change is made.

Routine extraction should not be carried out on individual pump components. It is sufficient to perform testing on resin batches. The relation between components and resin should be established during development.

932 This should read "water or other suitable solvents" (instead of "and") indicating that an appropriate single extraction solvent should be employed for routine extraction tests.

It should be sufficient for 3 incoming batches to be tested to confirm the suppliers results, combined with normal GMP/GLP audits of the plant/laboratory. The manufacturer should only need to test a representative number of batches since the process is validated.

940 Reference is made to ruggedness of a test procedure, which is not an ICH requirement. This specific reference, and others throughout the document, should be deleted.

953 Particle/droplet size distribution testing is product testing, not component testing.

955 The acceptance criteria must reflect the buying specification that the pump manufacturer will adhere to.

955 - 957	Clarification is needed on whether "clinical" means Phase III. This is the only way that the statement that the batches would all use identical valves would be reasonable.
972 - 1006	This section on Stability should simply cross-reference appropriate ICH guidelines and should adhere to the principles included in the ICH guidelines.
1020 - 1030	For test intervals, this guidance should just refer to ICH and the stability guideline.
1024	"accelerated test intervals of a minimum of four test time-points for 6 months". This is more restrictive than the ICH Q1A. Accelerated conditions are required to look for significant change and not used to set a shelf life, therefore, fewer time-points would be adequate.
1037 - 1040	Testing using different orientations can be done during development, and then the worst case can be chosen for future stability studies.
1061	There may be technical problems in controlling low humidity to the 15% level at 40C. Please explain the rationale for selecting these conditions.
1082	Clarification is needed on whether "clinical" means Phase III.
1094 - 1102	This section requires that the "source of excipients.. .used in these (stability) drug product batches should be specified." This seems to be an excessive requirement for a pharmacopoeia1 excipient and we recommend it be deleted.
1119 – 1127	There is no mention of the batch size that should be investigated on stability for use in determining expiration dating.
1121 - 1125	Please clarify if this implies that the commonly accepted practice of collecting 12 months of room temperature data and using statistical analysis to predict shelflife is no longer acceptable.
1136	It should not be necessary for a change of source of a pharmacopoeia1 excipient in a solution to require more stability.

1147 - 1150 This section generalizes the idea that bracketing and matrixing protocols may not be appropriate for some drug products discussed in this document. Many multi-volume products are homogeneous bulk products and very suitable for matrixing or bracketing studies. Please re-write the language in the section to make this option more of a possibility.

1163 - 1165 It seems excessive to require that the development type studies be conducted on three batches of commercial product. For some of the studies, one batch should be sufficient, and development studies are preferably performed before the final device is available as part of the device optimization and selection process. With appropriate justification, these earlier studies should be acceptable.

1170 - 1193 Please clarify that sections A and B are not applicable for unit dose products.

1177 - 1181 Define "multiple orientations" in this context.

1183 As stated in the USP, the rest period should be defined depending on dosing regimen.

1200 - 1202 The previously stated cycle of 3 cycles per day between +4°C to 40°C to +4° C for at least 4 weeks is felt to be an adequate stress test. Aqueous systems are not suitable for freezing.

We think that the proposed stress test is too extreme. Please justify the rationale.

1205 - 1207 Are all the tests detailed really necessary for a cycling study?

1278 - 1287 Please clarify that this section is not applicable for unit dose products.

1353 The inclusion of net content (fill) weight in the label of device-metered products may cause confusion since the fill weight may significantly exceed the nominal dose x number of doses.

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